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A STANDARDIZATION OF THE SANDMEYER REACTION, WITH SPECIAL APPLICATIONS[1]

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Introduction

Few reactions have been studied more extensively than Sandmeyer's reaction. Its literature records theoretical discussions and numerous descriptions of methods of conducting the reaction. The present investigation does not attempt to elaborate the theory but aims to develop (I) a standardized laboratory procedure which is generally applicable to aromatic amines, and presents (II) a quantitative study of the percentage theoretical yields obtained when the method is employed in the preparation of several series of disubstituted products of benzene, namely, (A) the *para* dihalogen benzenes, and (B) the *ortho, meta* and *para* dichloro-, chlorobromo-, chloronitro-, and bromonitrobenzenes. A cupric salt modification (III) of the standardized method is also presented.

According to Hantzsch and Blagden[2] the replacement of the amino group by a halogen atom or other radical in Sandmeyer's reaction involves the following reactions.

$$C_6H_5NH_3X + HNO_2 = C_6H_5N_2X + 2H_2O \qquad (1)$$
$$C_6H_5N_2X + CuY = C_6H_5Y + CuX + N_2 \qquad (2)$$

A review of the literature shows wide variations not only in the kind of acid used in the formation of the initial amine salt, but also in the quantities of acid, cuprous salt and amine. In the present investigation, which is primarily one of comparison of percentage yields obtained under identical conditions, many preliminary experiments showed acetic acid to be preferable to either hydrochloric or sulfuric for the formation of the amine salt, since (1) the acetates of the aromatic amines are in general relatively soluble, (2) frothing during addition to the cuprous salt was less, and (3) little tarry matter was formed.

In the proposed standardized method, the quantities of reagents used were in ratios corresponding to ten moles of acid, one mole of cuprous salt and one mole of amine. Possible variations due to catalytic effect and concentration changes were avoided by the use of a uniform amount of sodium nitrite slightly in excess of that required theoretically for diazotization. The initial use of one-eighth mole of the amine, giving a minimum

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[1] A synopsis of a thesis presented to the Faculty of the Graduate School, University of Cincinnati, by Irvine W. Grote in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Hantzsch and Blagden, *Ber.*, **33**, 2544 (1900).

calculated yield of 15 g. of the final product, afforded reproducible results and conveniently handled volumes.

I. Standardized Method

Cold Procedure (0–5°)

Preparation of the Amine Acetate and Diazotization.—One-eighth mole of the aromatic amine was dissolved in 250 cc. of 50% acetic acid, avoiding warming if possible. The solution was cooled to 0°, 50 g. of ice added, and 70 cc. of a 15% sodium nitrite solution introduced slowly below the surface of the acetate solution, accompanied by rapid mechanical stirring which was continued for 10 to 30 minutes after the addition of the nitrite solution had been completed.

Preparation and Action of the Cuprous Halide Solutions.—The cuprous solution containing one-eighth mole of cuprous salt (as CuX) and 1.5 moles of the corresponding halogen acid in 250 cc. of solution was placed in a 2-liter beaker surrounded by an ice-bath, cooled to 0° and 50 g. of ice added. The diazonium acetate solution was then added slowly through a wide funnel tube reaching to the bottom of the cuprous solution, the temperature kept below 5° and mechanical stirring continued for 30 minutes after the addition was completed. The mixture was then allowed to stand overnight.

Recovery of the Product.—The reaction mixture was steam distilled. When solid products were obtained, they were pulverized, shaken with 3% sodium hydroxide solution, washed with water, thoroughly dried, and melting points were determined. Liquid products were extracted, recovered, and boiling points checked.

Hot Procedure (100–105°)

In view of the conflicting statements by Sandmeyer[3] and Erdmann[4] upon the effects of temperature, the desirability of also applying the standardized method to the same amines at temperatures between 100° and 105° was investigated in order to compare the yields by both cold and hot procedures.

Hot Process Modification of the Standardized Method.—The sole modification of the process as before described consisted in adding the cold diazonium salt solution to the boiling cuprous solution contained in a 2-liter flask equipped with a 4-holed rubber stopper through which the following attachments were fitted: (1) a long reflux condenser; (2) a wide funnel tube reaching to the bottom of the flask through which the diazonium solution was added; (3) a thermometer with bulb immersed in the cuprous solution; (4) a steam inlet tube to provide both agitation and heat. The temperature during the process is easily kept at 100–105°. Heating and stirring were continued for ten minutes after the addition had been completed and the reaction mixture was steam distilled directly from the same flask.

II. Quantitative Study of Proposed Method

A. The *Para* Dihalogen Benzenes.—The following chart graphically summarizes the nine possible transformations effected by the standardized method when the amino group of chloro-, bromo- and iodo-aniline was substituted by chlorine, bromine and iodine, yielding the *six* possible *para* dihalogen benzenes.

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[3] Sandmeyer, *Ber.*, **23**, 1880 (1890).

[4] Erdmann, *Ann.*, **272**, 141 (1893).

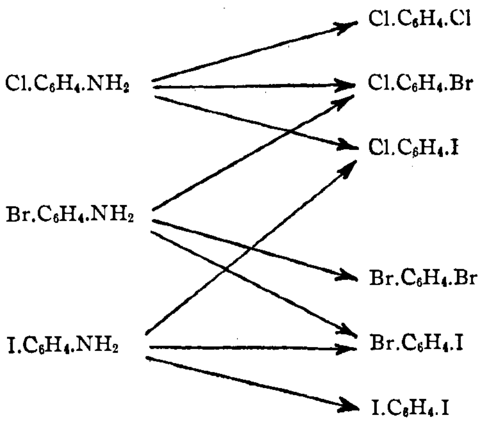

Table I records the percentage yield of each of the dihalogen products obtained in conformity with the foregoing scheme, each transformation being effected according to both the cold and the hot methods. The results obtained by the cupric salt modification, to be described later, are included for comparison.

Each value tabulated is the mean percentage, expressed as a whole number, of the results of two, and in some instances three, independent runs *differing from one another by not more than 3%, and in most cases less then 2%.*

TABLE I

PERCENTAGE YIELDS OF *p*-DIHALOGEN BENZENES FROM MONOHALOGEN AMINES

Initial *p*-amine	Halogen introduced	*p*-Dihalogen derivative	Yield, cold, 0–5°, %	Yield, hot, 100–105°, %	Cupric salt modification Yield, cold, 0–5°, %
$Cl.C_6H_4.NH_2$	Cl	$Cl.C_6H_4.Cl$	76	68	58
$Br.C_6H_4.NH_2$	Cl	$Br.C_6H_4.Cl$	74	68	42
$I.C_6H_4.NH_2$	Cl	$I.C_6H_4.Cl$	67	67	..
$Cl.C_6H_4.NH_2$	Br	$Cl.C_6H_4.Br$	83	82	88
$Br.C_6H_4.NH_2$	Br	$Br.C_6H_4.Br$	80	77	87
$I.C_6H_4.NH_2$	Br	$I.C_6H_4.Br$	81	73	..
$Cl.C_6H_4.NH_2$	I	$Cl.C_6H_4.I$	71	81	..
$Br.C_6H_4.NH_2$	I	$Br.C_6H_4.I$	72	78	..
$I.C_6H_4.NH_2$	I	$I.C_6H_4.I$	78	78	..

B. *Ortho-*, *Meta-* **and** *Para-***Dichloro-, Chlorobromo-, Chloronitro- and Bromonitro-benzenes.**—Steric influences were noted when the standardized procedure was extended to the replacement of the amino group in the *o*-, *m*- and *p*-chloro-anilines, and also in the *o*-, *m*- and *p*-nitro-anilines, by both chlorine and bromine. These reactions afford data as to the influence a change in the group attached to the ring may have. The yields of the final products are summarized in Table II. The values represent mean averages of two or more independent runs not differing more than 3%, as in Table I.

TABLE II

PERCENTAGE YIELDS OF THE CHLORINE AND BROMINE DERIVATIVES OF *o*, *m* AND *p*-CHLORO-ANILINES AND NITRO-ANILINES

Initial amine *o*, *m*, *p*	Halogen introduced	*o*, *m* and *p* product	Yield, *o*, %	Yield *m*, %	Yield, *p*, %
$Cl.C_6H_4.NH_2$	Cl	$Cl.C_6H_4.Cl$	48	49	75
$Cl.C_6H_4.NH_2$	Br	$Cl.C_6H_4.Br$	54	39	83
$NO_2.C_6H_4.NH_2$	Cl	$NO_2.C_6H_4.Cl$	73	59	72
$NO_2.C_6H_4.NH_2$	Br	$NO_2.C_6H_4.Br$	80	75	90

III. Cupric Salt Modification

The conflicting statements as to the results of substitution of cuprous salts by cupric[5] and others made it seem desirable to determine the comparative yields of the products obtainable when the standardized method was so modified.

Accordingly, one-eighth molar quantities of cupric chloride ($CuCl_2.2H_2O$) and cupric bromide ($CuBr_2$) were substituted for cuprous chloride and bromide, respectively, and the cold method was repeated with *p*-chloro- and *p*-bromo-anilines. (The instability or non-existence of cupric iodide makes its use impossible in this part of the investigation.) The transformations effected and yields obtained using cupric salts are given in Table I.

When the standardized method using *hot cupric solutions* was applied to the *para* halogen anilines, considerable quantities of azo compounds and much tarry matter were formed. The yields of dihalogen benzenes were so low (about 10%) that the study of the hot method with cupric salts was abandoned.

A brief note should be added that the standardized method has been applied to reactions with *p*-chloro-aniline in which the chlorides of iron (ferrous and ferric), cobalt, nickel, and manganese have been substituted for the cuprous halides. The yields of *p*-dichlorobenzene were found to range from 9 to 16% and are practically identical with the yields obtained when no catalyst whatever is used. Ferrous chloride is a noteworthy exception, however, in that with it a 43% yield was obtained.

Summary and Conclusions

Inspection of the data in Tables I and II seems clearly to warrant the following conclusions.

1. Chlorine, bromine and iodine introduced into the *para* halogen amines (Table I) give practically identical average yields of the dihalogen benzenes when the diazonium salt is added to either a *hot* or *cold* cuprous halide solution. The average yield for the nine possible replacements at 0° to 5° is 76%, as compared to 74% if the same replacements are made at

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[5] Contardi. *C. A.*, **17**, 2109 (1923); **19**, 827 (1925); *Ann. chim. applicata*, **7**, 13 (1923).

100° to 105°. The maximum difference in any single case was only 10%.

It is thus evident that the conflicting statements in the literature as to the relative merits of the hot and cold methods are probably due to the many varied conditions under which the Sandmeyer reaction has been studied. The standardized method, at least for the preparation of the *para* dihalogen benzenes, gives remarkably uniform and satisfactory results.

2. The character of the halogen atom already present in the *para* halogen aniline (Table I) or the presence of a nitro group as in *p*-nitroaniline (Table II) appears to have little if any effect upon the yield of the *para* halogen derivative.

3. The yields of the *ortho, meta* and *para* dihalogen benzenes (Table II) and the *o*-, *m*-, and *p*-chloro- and bromonitrobenzenes (Table II) are greatest when bromine, and least when chlorine replaces the amino groups. With the single exception that *m*-chloro-aniline (Table II) gave a greater yield of *m*-dichlorobenzene than of *m*-chlorobromobenzene, the general rule appears to hold that the yields of the substituted derivatives, from the point of view of the halogen atom introduced, follow the relative order Br > I > Cl. The variations, however, between the two extremes are slight in most cases.

4. The *o*- and *m*-chloro-anilines gave markedly lower yields of the corresponding dichloro- and chlorobromobenzenes than did the *para,* and some 25% lower than the corresponding products obtained from the nitroanilines. The respective isomeric products are formed, however, in both cases in the following relative quantitative order: *para* > (or =) *ortho* > (or =) *meta*.

5. Cupric chloride and bromide may be substituted satisfactorily for cuprous chloride and bromide in the standardized *cold* method as applied to the *para* halogen anilines. The yields (Table I) with *cupric chloride* are 20 to 30% *lower* than those obtained with *cuprous chloride.* Conversely, the yields with *cupric bromide* are 6 to 7% *higher* than those obtained with *cuprous bromide.*

6. The general rule indicated in (3) is even more marked when cupric salts are used in place of cuprous.

Further applications of the standardized method to other aromatic amines are planned. The effects of various salts as catalysts will also be investigated more fully.

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